EDA Assessment Report for human medicinal product

(Scientific Discussion)

Salcrozine Faes 500 mg & 1000 mg Gasrto Resistant Tablet

(Mesalazine)

Date: June, 2025.

I. Introduction

- Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Salcrozine Faes 500 mg & 1000 mg Gasrto Resistant Tablet
- The product is indicated for the treatment of inflammation caused by inflammatory bowel disease (ulcerative colitis and Crohn's disease)

II. Quality Aspect

Drug Substance

- CEPs from two suppliers have been submitted for evaluation.
- The drug substance is almost white or light grey or light pink powder or crystals, very slightly soluble in water, practically insoluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid.
- The drug substance specifications are Description, Identification (U.V, I.R & T.L.C), Appearance of solution, Reducing substances, Related substances (HPLC), Impurities A & C (HPLC), Impurity K (HPLC), Chlorides, Sulfates, Loss on drying, Sulphated ash, Assay, Bulk and Tapped density.
- Analytical methods are in line with the current version of the European pharmacopeia monograph and the certificates of suitability (CEP)
- The applicant provided batch analysis results of 3 batches from the first manufacturer and 3 batches from the second manufacturer. The results of all tests were well within specification limits and batch data was found acceptable.
- As per the CEP from the first supplier issued by the EDQM regarding the container closure system, the substance is packed in double polyethylene bags placed either in a cardboard box or a fiber drum.
- As per the CEP from the second supplier issued by the EDQM regarding the container closure system, the substance is packed in double polyethylene bags (outer black) placed in a polyethylene or paper or fiber drum.
- As per the CEP from the first supplier issued by the EDQM, the retest period of the drug substance is 2 years if stored, protected from light, in double polyethylene bags placed either in a cardboard box or a fiber drum.
- As per the CEP from the second supplier issued by the EDQM, the retest period of the drug substance is 5 years if stored in double polyethylene bags (outer black) placed in a polyethylene or paper or fiber drum.

Medicinal Product

- **Product Description**

For 500 mg:

-Oblong tablets, with homogeneous gastro-resistant orange coloured coating, containing 500 mg of mesalazine.

-The product is packed in: Al-Al thermoseleable blisters containing 10 tablets per blister.

For 1000 mg:

-Oblong tablets of 21.9 mm length and 10.9 mm of diameter, with homogeneous gastro-resistant orange coloured coating, containing 1 g of mesalazine.

-The product is packed in: PVC/PVDC/AL thermoseleable blisters containing 10 tablets per blister.

-The excipients for 500 mg are: Sodium carbonate, anhydrous, Glycine, Cellulose microcrystalline, Croscarmellose sodium, Silica, colloidal anhydrous, Calcium Stearate, Povidone (for tablet core) and Talc, Titanium dioxide, Methacrilic acid – Ethyl acrylate copolymer (Eudragit L-30 D), Macrogol 6000, Yellow ferric oxide (E-172), Red ferric oxide (E-172), Isopropyl alcohol, Purified water, Dibutyl sebacate, Povidone, Methacrilic acid – Methyl methacrylate copolymer (Eudragit L-12,5 P), Methacrilic acid – Methyl methacrylate copolymer(Eudragit S-12,5 P) (for tablet coat).

-The excipients for 1000 mg are: Sodium carbonate, anhydrous, Glycine, Cellulose microcrystalline, Croscarmellose sodium, Silica, colloidal anhydrous, Calcium Stearate, Povidone (K-30) (for tablet core) and Talc, Titanium dioxide, Methacrylic acid – Ethyl acrylate copolymer (1:1) Dispersion 30 per cent (Eudragit® L 30 D), Macrogol 6000, Yellow ferric oxide (E-172), Red ferric oxide (E-172), Dibutyl sebacate, Povidone (K-30), Methacrylic acid – Methyl methacrylate copolymer (1:1) (Eudragit® L 12.5), Methacrylic acid – Methyl methacrylate copolymer (1:2) (Eudragit® S-12.5) (for tablet coat).

- **Pharmaceutical development**

- The development of the product has been described, the aim was to develop a delayed release formulation that prevents release of the active ingredient in the gastric environment while allowing for rapid release of the active ingredient in the intestine region. The choice of excipients is justified and their functions explained.

- Overall, the choices of the packaging, manufacturing process, physicochemical properties and microbiological attributes are justified.

- **Manufacturing process**

- The manufacturing process consists of Granulation, Mixing and lubrication, Compression and Coating.

- The manufacturing process was adequately validated according to relevant guidelines from three commercial batches.

- **Control of excipients**

-All excipients comply with Ph.Eur except for Yellow ferric oxide (E-172), Red ferric oxide (E-172) and Dibutyl sebacate which complies with USP specifications.

- **Control of drug product**

- The specifications include the following tests: Appearance, Resistance to artificial gastric juice, Dissolution test, pH 6.4, 60 minutes, Dissolution test, pH 6.8, 30 minutes, Dissolution test, pH 6.8, 75 minutes (Spectrophotometry), Identification (UPLC and UV), Mesalazine content (UPLC), Related substances (UPLC), Residual Solvents (GC), Total aerobic microbial count/g, Total combined yeast and mold count/g, Escherichia coli/g

- Analytical methods were revised and found to be suitable for the required testing.

- Batch Analysis results from the proposed production site were provided for 8 batches (5 batches for 500 mg strength and 3 batches for 1000 mg strength). The results of all tests are well within specification limits and batch data is acceptable.

- **Container closure system**

- **<u>For 500 mg:</u>**

- The drug product is packed in AL-AL aluminium- aluminium heatsealed blisters of 10 tablets with Patient information leaflet in a cardboard outer box.

- **<u>For 1000 mg:</u>**

- The drug product is packed in (PVC/PVDC-AL) blisters of 10 tablets with Patient information leaflet in a cardboard outer box.

- **Stability**

- Stability of finished pharmaceutical products are submitted in accelerated (40°C ±2°C/75% RH ±5%) and long term (25°C ±2°C/60% RH ±5%), (30°C ±2°C/65% RH ±5%), (30°C ±2°C/75% RH ±5%), storage conditions. Detailed review was carried out for all stability indicating parameters and all found in line with their acceptance criteria throughout all time intervals. The provided stability study supports the proposed shelf life of 4 years when stored at a temperature not exceeding 30̊C.

- **Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies**

- Declarations/certificates of TSE/BSE free are submitted for excipients used in the manufacturing of salcrozine Faes 500 mg & 1000 mg Gastro resistant tablets.

Summary basis of opinion:
Based on the review of CTD quality module and other supplementary documents; from the quality point, the product is approved

III. Non-Clinical &IV. Clinical Aspects

No new preclinical data have been submitted with this application. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application. An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

Introduction

Mesalazine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.

Mesalazine is indicated for the treatment of mildly to moderately active ulcerative colitis in adults and patients 5 years or older. Mesalazine is also indicated for the maintenance of remission of ulcerative colitis in adults and maintenance of remission of Crohn's ileocolitis.

*Summary of Listing of Clinical Studies of Mesalazine 500mg

- Study Title:

***Screen the in vitro performance of Mesalazine 500 mg**

- Report Klein 2015, In vitro dissolution studies simulating a gastrointestinal passage with a continuous and discontinuous fasted small intestine passage

*** Evaluate the pharmacokinetics of 5-ASA**

-Report Linkoping Study Randomized, open cross-over study Subjects received four single doses of 5-ASA not less than one week apart.

***Bioavailability (BA)& Bioequivalence Study Reports:**

-5-ASA/A04-GER, Each subject was studied on 2 occasions, at 5-7 balanced cross-over design, with randomly allocated treatment sequence.

*** Evaluate the safety and efficacy of Mesalazine**

- ASA-MCT-19A , Multi-center, double-blind, randomized, active controlled.

*Summary of Listing of Clinical Studies of Mesalazine1000mg :

- Study Title:

***Bioavailability (BA)& Bioequivalence Study Reports:**

-5-ASA/A04-GER, Each subject was studied on 2 occasions, at 5-7 balanced cross-over design, with randomly allocated treatment sequence.

*** Evaluate the pharmacokinetics of 5-ASA**

-Report Linkoping Study 1988 Randomized, open cross-over study Subjects received four single doses of 5-ASA not less than one week apart.

*** Evaluate the safety and efficacy of Mesalazine**

- ASA-MCT-19A , Multi-center, double-blind, randomized, active controlled

***Comparative bioavailability of Mesalazine 500 mg and Mesalazine 1 g formulations under fasted conditions**

- Study CLEU-0218_BAFAST, Single centre, phase I, single oral dose, open and randomised, two sequence, two treatment and four periods cross-over replicate bioavailability clinical trial with blind determination of the human plasma concentrations of mesalazine from the administered formulations under fasted condition

***Comparative bioavailability of Mesalazine 500 mg and Mesalazine 1 g formulations under fed conditions**

-Study CLEU-0118_BAFED, Single centre, phase I, single oral dose, open and randomised, two sequence, two treatment and four periods cross-over replicate bioavailability clinical trial with blind determination of the human plasma concentrations of mesalazine from the administered formulations under fedcondition

***Based on the clinical study Salcrozine Faes 500 mg & 1000 mg Gasrto Resistant Tablet submitted to EDA, found to recommend the approval of the marketing authorization of product.**